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Clinical Trial to Optimize Lymphoma Treatment in Uganda



UCI-Fred Hutch Cancer Centre, Kampala, Uganda. Photo by Jiro Ose for Fred Hutch

Global Oncology at Fred Hutchinson Cancer Research Center and the Uganda Cancer Institute are conducting a novel, early-phase clinical trial in Uganda that aims to improve cure rates for children and adults with two aggressive forms of lymphoma — Burkitt lymphoma and diffuse large B-cell lymphoma — as well as Kaposi sarcoma herpesvirus [KSHV]-associated multicentric Castleman's disease. Global Oncology launched the study in 2019 to evaluate a formulation of the monoclonal antibody against CD20, rituximab, that can be administered under the skin of cancer patients.

The project capitalizes on a collaboration of over a decade between Fred Hutch and the UCI, a site of landmark discoveries about endemic Burkitt lymphoma and its association with Epstein-Barr virus. Now, the organizations are forging new partnerships and developing world-class clinical trials infrastructure to accelerate research on high-impact cancer therapies in

Uganda. This study is the next step following a project implemented by Fred Hutch and the UCI on research and clinical-care quality improvement for Burkitt lymphoma patients at the UCI.

THE CURRENT STATE OF LYMPHOMA THERAPY IN UGANDA

The commonest lymphomas in Uganda, Burkitt lymphoma and diffuse large B-cell lymphoma, occur in children and young adults. These cancers are lethal if untreated but largely curable with relatively short courses of therapy. However, appropriate diagnosis and therapy and adequate supportive care are required. Currently Burkitt lymphoma is treated in Uganda with a 50-year-old chemotherapy regimen. Continuing to use this regimen will limit progress toward increasing cancer survival. While the one-year survival for Burkitt lymphoma has risen to more than 50% at the UCI, the use of contemporary chemotherapy

SPOTLIGHT ON LYMPHOMA IN UGANDA

- Lymphoma is one of the most common cancers in Uganda and the second most common cause of cancer death in children and young adults.
- Many lymphomas in Uganda are associated with viruses, such as Epstein-Barr virus and KSHV, that are nearly ubiquitous in Uganda and transmitted in early childhood. Importantly, EBV- and KSHV-associated lymphomas are curable.
- Approximately 1.6 million people in Uganda are infected with HIV, which makes them over ten times more likely to be diagnosed with lymphoma. At the UCI, 30% of lymphomas occur in patients who are HIV-positive.
- Many cases of diffuse large B-cell lymphoma and nearly all cases of endemic Burkitt lymphoma are EBV-related.
- KSHV can cause a life-threatening lymphoproliferative disease called multicentric Castleman disease (also called KSHV-MCD) that can be effectively treated with rituximab.
- Fred Hutch and the UCI aim to deliver high-quality treatment and care by linking cancer and HIV care and to provide curative therapy where possible regardless of a patient's HIV status.

regimens in the U.S. results in a cure rate of over 90% for patients with Burkitt lymphoma. Likewise, diffuse large B-cell lymphoma in Uganda is treated with a regimen of four drugs known as CHOP. However, this regimen is over 20 years old and its use as a sole treatment is associated with suboptimal outcomes.

In the U.S., the drug rituximab has revolutionized the treatment of certain forms of non-Hodgkin lymphoma, including diffuse large B-cell lymphoma, Burkitt lymphoma and KSHV-MCD. Rituximab was developed originally for administration via an intravenous infusion, typically over a period of two to six hours. U.S. oncology clinics depend on infusion pumps and nurses trained in administering and monitoring infused cancer therapies, both of which are unavailable in most of Africa. Added to the barrier posed by drug costs, barriers to administration limit access to this and many other scientifically promising therapies.

A POTENTIAL DISRUPTOR FOR AGGRESSIVE B-CELL LYMPHOMAS IN AFRICA

In 2017, the U.S. Food and Drug Administration approved rituximab hyaluronidase that can be delivered by subcutaneous injection over the course of five to six minutes, eliminating the need for infusion pumps and long infusion times. This innovation in drug delivery could dramatically reduce delivery times and further facilitate the drug's application in low-resource settings.

Rituximab has significantly improved survival rates of adults with non-Hodgkin lymphoma, specifically those with diffuse large B-cell lymphoma. Originally developed for adult lymphoma, rituximab has a more recent body of evidence supporting its use in pediatric Burkitt lymphoma. A 2016 clinical trial of rituximab added to standard treatment



TOP: Diana Basemera, histology technician, examines a tissue sample at the UCI-Fred Hutch Cancer Centre, November 2016. Photo by Robert Hood / Fred Hutch. **ABOVE:** Dr. Charles Babutunga examines Brenda Nakimera, 9, in November 2016 at the UCI-Fred Hutch Cancer Centre as her mother Leticia Nakayenga looks on. Photo by Jiro Ose for Fred Hutch.

in children in the U.S. and Europe with high-risk Burkitt lymphoma was stopped early because the regimen showed extraordinary efficacy over the current standard of care alone. In this trial, rituximab also had an extremely safe profile. Rituximab is now included on the World Health Organization's "Model List of Essential Medicines."

A CLINICAL TRIAL TO OPTIMIZE LYMPHOMA TREATMENT

Given the tremendous lifesaving potential of using subcutaneous rituximab to address the lymphoma cancer burden in children, adolescents and adults in Africa, Fred Hutch is partnering with the UCI to conduct an important safety and feasibility study in a local African context and determine an appropriate dose for children. The investigators anticipate that the outcomes from this study will help transform lymphoma care throughout sub-Saharan Africa and other resource-limited settings.

Over three years, Global Oncology's clinical trial will evaluate the safety and effects of subcutaneous rituximab in treating patients with Burkitt lymphoma, diffuse large B-cell lymphoma and KSHV-MCD. The primary goal is to evaluate the safety and pharmacokinetics of the new formulation of rituximab, including the optimal dosage in children. The study aims to enroll 36 patients at the UCI. Once safety is established in adults, the trial will expand to adolescents and children. Patients with Burkitt lymphoma or diffuse large B-cell lymphoma will receive rituximab in combination with UCI's current standard first-line chemotherapy regimen and KSHV-MCD patients will receive rituximab alone.

Led by Dr. Thomas Uldrick (deputy head, Fred Hutch Global Oncology), Dr. Henry Ddungu (consultant, Hematology/Oncology, UCI), and Dr. Joyce Balagadde Kambugu (consultant, pediatric oncology



Lazarus Okoche prepares a specimen at the UCI-Fred Hutch Cancer Centre's molecular diagnostic lab. Photo by Jiro Ose for Fred Hutch

gist and head, Pediatric Oncology, UCI), the all-Ugandan clinical research team in Kampala receives ongoing, advanced training on clinical trials implementation and cancer patient care. The trial will also allow the research team to conduct a preliminary assessment of its efficacy as a platform for other translational studies to help us better understand the unique biology of Burkitt lymphoma in Africa.

Optimizing treatment, while also strengthening diagnosis and supportive care, is one of the best ways to drastically improve the survival of young patients with Burkitt lymphoma and the survival of adolescents or adults with other lymphomas. If this study's findings show promise, larger multi-center efficacy trials in Africa may be warranted. Thus, this first step could lead not only to improved outcomes for patients in Uganda but to the wider use of rituximab in lymphoma patients across sub-Saharan Africa, helping make progress towards the United Nations Sustainable Development Goal

to reduce premature mortality from non-communicable diseases, including cancer, by 2030.

Fred Hutch continues to be at the forefront of global cancer research to ensure that advances in cancer treatment are available to all patients globally, especially in low-resource settings. This project is made possible through support from Fred Hutch, Roche, the Burkitt Lymphoma Fund for Africa and other private donors. Fred Hutch Global Oncology invites new collaborators and contributors to join the important movement to advance treatment options and reduce the cancer burden in Uganda and elsewhere.

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